

Health Update: Nitrogen Dioxide Exposure Increases Allergic Responses in Asthmatics

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California Air Resources Board

California Environmental Protection Agency

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Thank you Ms. Witherspoon. Good morning, Dr. Sawyer and members of the Board. Staff from ARB and the Office of Environmental Health Hazard Assessment are currently reviewing the State ambient air quality standard for nitrogen dioxide, NO₂ for short, which was last reviewed in 1992. The current review was mandated by the Children's Environmental Health Protection Act (Senate Bill 25), which required that all State ambient air quality standards be prioritized for review to ensure that they adequately protect public health, particularly that of infants and children. Staff will be bringing you recommendations for revising the NO₂ standard later this year.

Nitrogen Dioxide (NO₂) Standard

- Ambient air quality standards
- Define maximum safe exposures
- Protect vulnerable sub-populations
- NO₂ standard last reviewed in 1992
 - 0.25 ppm, one-hour average
- Asthmatics identified as vulnerable

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As Ms. Witherspoon mentioned, ambient air quality standards define a maximum safe exposure.

One of the key considerations in ambient air quality standard review is identifying sub-populations that may be more vulnerable to air pollutants than the average, such as asthmatics and children, so that the standards can adequately protect them.

The result of the 1992 standard review was that the Board retained the existing one-hour standard of 0.25 ppm. Asthmatics were identified as a vulnerable group with reference to NO₂ in the course of the standard review.

As you know, the health effects of air pollution on asthmatics has been a concern of the Board for some time. To give you a perspective on the magnitude of this issue, over 300,000 California residents visited the emergency room in 2001 because of their asthma.

Today we will discuss a key paper identified in our review that suggests that the existing NO₂ standard does not adequately protect asthmatics.

Background

- Controlled exposure and epidemiologic studies do not agree
- Controlled human studies
 - Clinical effects of NO₂ – above 0.5 ppm
 - Reduced lung function
 - Symptoms: cough, chest tightness
 - No effects at level of standard
- Epidemiologic studies – acute effects at concentrations <0.25 ppm
 - Asthma exacerbation
 - Increased asthma medication use
 - Hospitalization and emergency room visits
 - Premature mortality

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Health effects of air pollution are investigated using several approaches. In the case of NO₂, results from controlled exposure studies and epidemiologic studies do not agree.

Controlled exposure studies involve exposure of humans to a fixed amount of pollutant in an enclosed chamber. This type of study usually focuses on effects such as lung function and symptoms. Controlled studies investigating the health effects of NO₂ have found significant changes in symptoms or lung function in normal or asthmatic subjects only with exposure to concentrations of NO₂ above 0.5 ppm.

In contrast, epidemiologic studies, which investigate responses on a population level, have demonstrated statistical associations between health effects and NO₂ concentrations at and below the current standard of 0.25 ppm. These effects include various indicators of asthma exacerbation, such as emergency room visits, decreased lung function, increased symptoms, and increased medication use. Epidemiologic studies have also associated ambient concentrations of NO₂ with hospitalizations and emergency room visits for heart and lung disorders, and premature mortality.

The effects I have just discussed are termed clinical effects because they are relatively obvious effects, and can be measured with standard medical tests.

How Does NO₂ Exacerbate Asthma?

- Sub-clinical effects of NO₂ – below 0.3 ppm
 - Increased airway reactivity
 - Increased airway inflammation
 - Increased response to allergen in asthmatics
- Sub-clinical effects may explain epidemiologic findings

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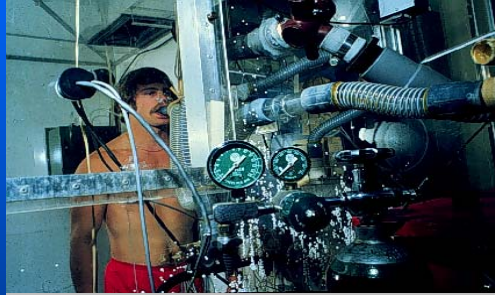
On the previous slide we saw that at similar NO₂ concentrations controlled exposure studies showed no effects while epidemiologic studies did. This presents the question: How does NO₂ exacerbate asthma?

NO₂ is an oxidant pollutant, like ozone, although it is considerably less potent in causing effects. Several studies suggest that NO₂ may induce subtle effects in asthmatics that do not show up in ordinary medical tests. These are termed sub-clinical effects, and are generally present without our recognizing them. Sub-clinical effects that have been observed with NO₂ exposure include increased airway reactivity, increased airway inflammation, and increased response to allergen, all of which are features of asthma.

Some researchers have suggested that these subtle effects could worsen asthma to the point that clinically important effects, such as increased medication use, emergency room visits or hospitalization result.

The Question

Does NO₂ exposure lead to increased allergic inflammation in the airways of asthmatics?



Barck, C., J. Lundahl, G. Hallden, and G. Bylin. Brief exposures to NO₂ augment the allergic inflammation in asthmatics. *Environmental Research*. 97: 58-66, 2005

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These results lead to the question: does NO₂ exposure increase allergic inflammation in the airways of asthmatics? The paper we are considering today is a controlled human exposure study that investigated this question. It is entitled “Brief exposures to NO₂ augment the allergic inflammation in asthmatics”, by Barck and colleagues from the Karolinska Institute in Stockholm, Sweden. The paper, published in 2005, explored the hypothesis that nitrogen dioxide exposure increases allergic responses in the lungs of asthmatics who undergo an allergen challenge several hours after nitrogen dioxide exposure.

Methods

- Subjects: 18 mild, allergic asthmatics (timothy grass or birch tree pollen)
- Exposures: NO₂ (0.26 ppm) or clean air
 - Three-day protocol
 - 15-minute exposures
- Endpoints (pre- and post-exposure)
 - Symptoms (i.e., cough, chest tightness)
 - Lung function
 - Inflammatory cells in sputum and blood
 - Inflammatory mediators in sputum and blood

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The subjects in this study were 18 mild asthmatics who were allergic to timothy grass or birch tree pollen.

Each subject participated in exposures to filtered air and 0.26 ppm nitrogen dioxide, with each of the two experimental sessions conducted over a three day period.

On the first day, the subjects inhaled filtered air or nitrogen dioxide for 15 minutes, followed 3 to 4 hours later by an allergen inhalation challenge. On the second day, the subjects inhaled the same atmosphere for two 15 min periods followed by a second allergen challenge.

Endpoints, including symptoms, lung function, inflammatory cells and biochemicals in sputum and blood were measured pre- and post exposure on each day, and on the morning of Day 3.

Results

- No changes in:
 - Lung function, symptoms, or number of inflammatory cells
- Enhanced allergic response with NO₂ exposure – sub-clinical effect
 - Evidence for allergic cell activation (eosinophils)
 - Activation marker increased 6-fold in sputum and 2-fold in blood

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As seen in previous studies, there were no changes in lung function or symptoms in response to either the air-allergen or NO₂-allergen exposures.

However an intriguing and important sub-clinical effect did occur. While there was no change in the number of inflammatory cells in the lungs, one type of inflammatory cell, the eosinophil, was activated following the NO₂ exposure and not the filtered air exposure. Eosinophils are a special type of immune cell that is involved in allergic responses. When these cells are activated they release a protein that initiates allergic inflammation. The concentration of this protein increased about 6-fold in sputum and 2-fold in blood with NO₂ exposure, compared to filtered air exposure.

As noted earlier, previous controlled human studies suggest asthmatics do not have significant responses to exposure to NO₂ alone. These results suggest that NO₂ and allergen interact in a way that amplifies allergic responses in the lungs of allergic asthmatics.

Conclusions and Implications

- Short NO₂ exposures can amplify allergic responses in asthmatics
- Plausible explanation for asthma exacerbation with NO₂ exposure
- Current CA ambient air quality standard for NO₂ has no margin of safety

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The findings of this paper lead to several conclusions.

First, that NO₂ exposure amplifies allergic responses in the lungs of allergic asthmatics. This is important in that the majority of asthmatics have allergic asthma, and simultaneous NO₂ and allergen exposure is the typical exposure pattern in the real world.

Next, amplification of allergic responses provides a biologically plausible explanation for epidemiologic findings of asthma exacerbation with NO₂ exposure.

Finally, these results, along with those of several other papers led Staff to conclude that the existing State NO₂ standard has no margin of safety and should be revised.

The draft staff report and recommendations for the state NO₂ standard were released for public comment on April 14. The Office of Environmental Health Hazard Assessment has recommended that the NO₂ standard be lowered, and Staff will be bringing you recommendations for revision of the standard later this year.

Thank you for your attention. Staff would be happy to answer any questions you may have.